Comparison of Development of Heterotopic Ossification in Injured US and UK Armed Services Personnel With Combat-Related Amputations: Preliminary Findings and Hypotheses Regarding Causality

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Background: Recent reports have documented the rate of heterotopic ossification (HO) formation in the residual limbs of combat-related amputees from the US Armed Forces injured in Operations Iraqi and Enduring Freedom. Final amputation level within the zone of injury and blast as the mechanism of injury were identified as possible risk factors for the occurrence and grade of HO. There has been no previous description of HO in combat-related amputees from the UK service personnel. The purpose of this study was to examine potential differences in the prevalence of HO between UK and US Allied Forces, with particular attention to these risk factors, patient exposures, and any treatment differences between these two groups.

Methods: We reviewed the medical records and radiographs of 35 combat-related amputations from the UK and contrasted them with 213 previously reported amputations in US military personnel. We evaluated prevalence and severity of residual limb HO, Injury Severity Score (ISS), the mechanism and zone of injury, type and level of amputation, number of debridements, method of wound irrigation, presence of severe head injury and/or burns injury, use of topical negative pressure therapy and pulse lavage, number of days until wound closure, type of closure, and subsequent infections. All patients had a minimum of 2-month posthospital discharge radiographic follow-up. Comparisons were made using Fisher's exact, one-way analysis of variance, and χ^2 analyses.

Results: There was no significant difference in either the overall prevalence of HO or the prevalence of moderate to severe HO in the two populations. Twenty of 35 (57.1%) limbs in the UK amputations developed HO compared with 134 of 213 (63%) in the US amputations ($p > 0.05$). The UK amputations had 12 cases (34.3%) of moderate to severe HO compared with 72 cases (33.8%) in the US amputations ($p > 0.05$). However, there was a significant difference in the number of UK amputations 0 of 20 (0%) versus the number of US amputations 25 of 134 (12%; $p = 0.04$), which required excision of symptomatic lesions. There was a significant association in the development of HO in UK personnel with the use of topical negative pressure treatment ($p = 0.05$) and increasing ISS scores ($p = 0.04$) and in the development of moderate to severe HO with increasing ISS ($p = 0.006$) and severe HI ($p = 0.04$). Unlike in the previous report, no significant association was found in UK personnel between any of the remaining hypothesized risk factors and either the presence or grade of HO.

Conclusions: Although no difference was identified in the overall prevalence of HO, there are inconsistencies in the possible underlying causes of HO between the two cohorts. Further research is required in an ongoing effort to determine a causal relationship between treatment and subsequent HO formation.

Key Words: Heterotopic ossification, Risk factors, Amputation level, Blast, Patient exposure.

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Heterotopic ossification (HO) is the formation of bone outside the skeletal system. It can be secondary to genetic causes such as fibrodysplasia ossificans progressiva, trauma (including burns), surgery for hip arthroplasty or treatment of elbow and acetabular fractures, and neurologic injury.[1,2] The pathogenetic factors involved are believed to be an inciting event, with an accompanying signal from the site of injury, a supply of mesenchymal cells with uncommitted genetic machinery, and an environment supportive of heterotopic bone production.[1,2]

Considering traumatic injuries, and amputations in particular, there are historical reports of HO in association with combat-related amputations.[3,4] However, these accounts have been sporadic over the last century, and the prevalence of HO in these populations remains unknown. More recently, a high incidence of HO has been reported in amputations from combat in US military personnel.[5] This incidence is considered secondary in part to the use of high-energy missiles and explosive devices in the ongoing conflicts in the Middle East, which have resulted in devastating wounds in patients with multiple injuries frequently associated with either traumatic or early surgical amputations.

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Complications of HO include debilitating residual limb pain from bony spicules and infection. This pain may substantially hinder rehabilitation by interfering with the fit of the prostheses or by limiting joint movements and may require excision of lesions for symptomatic relief.[6] Clearly, there is a need to prevent, or limit to the greatest extent possible, the development of HO by identifying and minimizing the risk factors.

Unfortunately, there is still considerable debate about the underlying etiologic factors for development of HO in these patients.[1,2] The previous investigation of combat-related amputees found that significant predictors of HO were final amputation level within the zone of injury (ZOI), which was also predictive of HO severity, and blast mechanism of injury (MOI).[5] These authors also identified differences in the severity of HO between none to mild and moderate to severe with regard to number of procedures and time to closure of the overlying wound. However, there have been no subsequent studies to substantiate this evidence or further elucidate these putative relationships. In addition, to date, there have been no reports on the incidence and possible underlying risk factors for HO in combat-related amputees from UK Armed Services personnel and, therefore, no comparisons of the UK and US populations of combat-related amputees for differences and/or similarities in the development of HO.

The purpose of this study was to compare differences in the prevalence, MOI, and treatment modalities in the development and severity of HO in UK and US Armed Services personnel with combat-related amputations. All patients were drawn from populations whose demographics have been previously described.[7,8]

This study hypothesized the following: (1) there are differences in the rate of HO between the UK and US combat-related amputee populations, (2) there are differences in practice in the management of amputees between the UK and US Armed Services; and (3) these differences in practice may affect the rate and severity of HO in these patients.

MATERIALS AND METHODS

We conducted a retrospective study using medical records and radiographs of wounded service members from the UK and the US for the time period 2001 to 2008. We used a previously published dataset for the US population[5] (September 11, 2001, to November 30, 2005) and gathered the UK data up to the current point (August 12, 2003, to May 1, 2008). Appropriate ethical approval was gained for both studies from their respective institutions. The data from the UK patients was designated as group 1 and the data from the US patients as group 2.

Combat-related amputations (35 UK and 213 US) were identified from their respective rehabilitation centers. The clinical records of all patients reviewed. Basic demographic data collected for both groups included patient age, sex, Injury Severity Score (ISS), MOI and ZOI, and date of injury. Data on the presence of traumatic brain injury (TBI), burns, and use of negative pressure wound therapy (NPWT) were also available for group 1 and Extremity Abbreviated Injury Score (EAIS) for group 2. For both groups, specific patterns of injury were documented, including type and level of amputation, number of debridements, number of days until wound closure, type of closure, and any subsequent infections. Follow-up radiographs at 6 months for group 1 and at 2 months for group 2 were obtained retrospectively from outpatient follow-up clinics or, for group 1, prospectively during their inpatient stay or as part of their review at their rehabilitation center.

All the radiographs for both groups were reviewed. HO presence and severity were classified according to the previously described classification system[5] (Fig. 1). Direct comparisons were made between points common to both databases according to the rate of HO, MOI, and treatment modalities (level of amputation, number of debridements, number of days until wound closure, type of closure, and use of NPWT) and the development and/or the severity of HO. For points present in only one database (severe burns and TBI), statistical analyses were made on the development and/or severity of HO.

Statistical Analysis

Descriptive statistical analyses were performed for all groups, and potential differences between rates and proportions of occurrences with development and severity of HO were assessed by using the χ^2 analysis. Group 1 and group 2 data were compared by using Fisher's exact test and Student's *t* test where appropriate. For group 1, one-way analysis of variance was used to assess the differences in the number of irrigation and debridement procedures and in the number of days from injury to definitive closure with development and severity of HO. A regression analysis was used to identify which factors had overall correlation to the development in HO between the two populations. The two data sets were pooled to assess the influence of the number of debridements and days to closure of the wound to the development of HO. The *t* test was used for this analysis, and significance was set at a p value of <0.05.

RESULTS

We identified 35 UK combat-related amputees (group 1) in comparison with the 213 previously reported US combat-related amputees (group 2). In group 1, the median age was 25 years (range, 18–42 years), and the median ISS was 10 (range, 4–59); for group 2, the average age was 26.0 years (range, 18–57 years), and the median ISS was 17 (range, 1–38). See Table 1 for a comparison of groups 1 and 2.

- None: No soft-tissue mineralization was evident on radiographs made at least 2 months after the injury.
- Mild: Ectopic bone occupied an estimated <25% of the cross-sectional area of the residual limb on either the anteroposterior or lateral radiograph.
- Moderate: Ectopic bone occupied 25% to 50% of the cross-sectional area of the residual limb on either the anteroposterior or lateral radiograph.
- Severe: Ectopic bone occupied >50% of the cross-sectional area of the residual limb on either the anteroposterior or lateral radiograph.

Figure 1. Grading of HO (based on single radiographic view of residual limb that demonstrated the greatest amount of ectopic bone).

TABLE 1. Comparison of Groups 1 and 2

	Group 1 (Total n = 35), n (%)	Group 2 (Total n = 213), n (%)	*p*
MOI			
Blast	33 (94.29)	187 (87.79)	0.39
Nonblast	2 (5.71)	26 (12.21)	
Amputation			
In ZOI	17 (48.57)	166 (77.93)	0.0003*
Above ZOI	18 (51.43)	47 (22.07)	
Amputation due to blast injury			
In ZOI	16 (45.71)	145 (68.08)	0.0004*
Above ZOI	17 (45.57)	41 (19.25)	
Amputation due to nonblast injury			
In ZOI	1 (2.86)	21 (9.86)	0.43
Above ZOI	1 (2.86)	6 (2.82)	
HO			
None	14 (40)	79 (37.09)	0.74
Mild	9 (25.17)	62 (29.11)	0.68
Moderate	9 (25.71)	37 (17.37)	0.24
Severe	3 (8.57)	35 (16.43)	0.23
Any occurrence	21 (60.00)	134 (62.91)	0.74
No. irrigation and debridements			
Mean	4.06	6.46	0.00003*
Median	4	6	
Range	1–9	2–20	
Days to closure			
Mean	14.49	17.33	0.007*
Median	9	15	
Range	2–57	4–57	
Method of closure			
Direct	18 (51.43)	149 (70)	0.03*
SSG/flap	17 (48.57)	64 (30.05)	
Absent	19 (54.29)	0 (0)	

* Values of significance ($p < 0.05$).

Rate of HO

There was no significant difference ($p = 0.74$) in the overall prevalence of HO between group 1 (60%; 21 of 35) and group 2 (62.9%; 134 of 213) or in the prevalence of severe HO ($p = 0.23$) between group 1 (8.6%; 3 of 35) and group 2 (16.4%; 35 of 213). The rate of severe HO in group 2 was nearly double the rate in group 1, but these results were not significant because of the small sample size in group 1.

MOI: Blast Versus Nonblast

There was no overall difference in the MOI between the two groups ($p = 0.39$). No significant association was found in group 1 between blast MOI and either the presence ($p = 0.82$) or grade ($p = 0.82$) of HO (see Table 3). A correlation analysis for group 1 showed a positive but weak relationship between blast MOI and group 1 ($R = 0.285$).

Treatment Modalities

Treatment modalities included the following.

Level of Amputation: In Versus Above ZOI

Group 2 had significantly more amputations ($p = 0.0003$) in the ZOI than group 1. Furthermore, group 2 had significantly more amputations in the ZOI ($p = 0.0004$) in blast limbs. No significant association was found in group 1 between final amputation in the ZOI and either the presence ($p = 0.85$) or grade ($p = 0.903$) of HO (Table 3). A correlation analysis for group 1 showed a weak positive correlation between amputation above the ZOI and group 1 ($R = 0.232$).

Number of Debridements

Group 2 had significantly more debridements ($p = 0.00003$) than group 1. There was an overall trend ($p = 0.078$) in group 1 for an increase in the severity of HO with an increase in number of debridements (Table 4). When groups 1 and 2 were combined, there was a significant association between the development of HO and the number of debridements ($p = 0.0082$).

Number of Days Until Wound Closure

Group 2 had significantly more overall number of days until wound closure ($p = 0.007$). Similarly, there was an overall trend ($p = 0.054$) in group 1 for development of HO with an increase in the number of days until wound closure (Table 4). When groups 1 and 2 were combined, there was a significant association between the development of HO and the number of days to wound closure ($p = 0.0122$).

Type of Closure: Direct Versus Split Skin Graft/Flap

There were significantly more direct closures in group 2 ($p = 0.03$) than in group 1. No significant association was found in group 1 between the type of closure and either the presence or grade of HO (Table 3).

Use of NPWT: Yes Versus No

The use of NPWT was not consistently recorded for group 2. There was a significant association ($p = 0.05$) in the development of HO in group 1 with the use of NPWT (Table 3).

Excision Symptomatic Lesions

There were significantly greater ($p = 0.048$) numbers of amputations that required excision of symptomatic lesions in group 2 (25 of 134, 12%) compared with group 1 (0 of 21, 0%).

Injury Severity Score

Table 2 provides ISS data on the severity of HO. There was a significant association in the development of HO with increasing ISS scores ($p = 0.04$). There was also a significant association in the development of moderate to severe HO with increasing ISS ($p = 0.006$). There was no difference in the ISS with increasing numbers of debridements ($p = 0.311$) or days to closure ($p = 0.421$; Figures 2 and 3).

TABLE 2. Analysis of Associations Between Development or Severity of HO and ISS

	HO	None	Mild	Moderate	Severe	None vs. Any	None/Mild vs. Moderate/ Severe
ISS	Mean	19.2	16.75	37.67	36.3	0.041*	0.0062*
	Median	17	20	42	42		
	Range	13–45	5–41	14–59	25–42		

* Values of significance ($p < 0.05$).

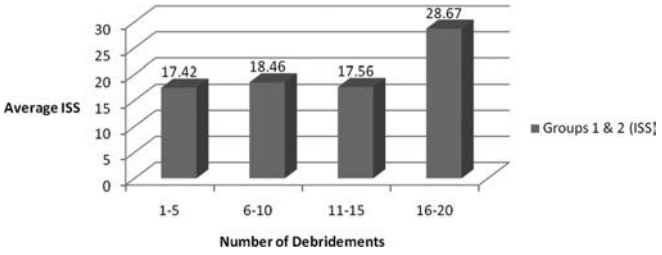

Figure 2. The association between the ISS and the number of debridements: no difference in ISS between groups ($p = 0.7894$).

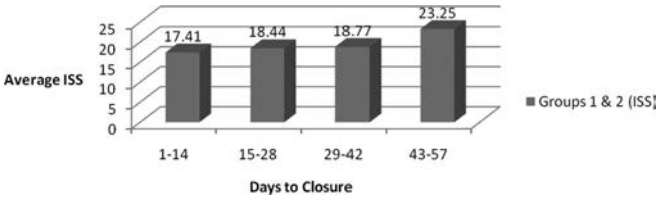

Figure 3. The association between the ISS and the time to closure: no difference in ISS between the groups ($p = 0.6287$).

TABLE 3. Group 1 Analysis of Associations Between Development and Severity of HO

	No HO vs. Any HO (*p*)	None/Mild HO vs. Moderate/Severe HO (*p*)
MOI (blast/GSW)	0.8184	0.82
Amputation level (in/above ZOI)	0.8452	0.903
Type of closure (direct/SSG)	0.3796	0.903
NPWT	0.050*	0.28
Severe burns	0.2072	0.63
TBI	0.2072	0.044*

GSW, gunshot wound.
* Values of significance ($p < 0.05$).

Group 1 Further Analysis

1. Severe burns: No significant association was found in group 1 between either the presence ($p = 0.21$) or the grade ($p = 0.63$) of HO (Tables 3 and 4).
2. TBI: There was a significant association in group 1 in the development of moderate to severe HO and TBI ($p = 0.044$).

Group 2 Further Analysis

EAIS: There is no difference in the AIS with increasing numbers of debridements ($p = 0.2455$) or days to closure ($p = 0.2656$; Figures 4 and 5).

DISCUSSION

As with previous conflicts, the extremities remain the most common sites of combat injuries in current military operations in Iraq and Afghanistan,[8] with 82% of patients sustaining extremity injuries. The high-energy injuries seen after blast or gunshot wounds are associated with significant damage to soft tissue and bones.[9,10] Despite modern medical advances, amputation remains a commonly performed procedure in the practice of war-time medicine,[11] and traumatic amputations remain frequent in the current wars. In both the US and the UK, there are dedicated amputee rehabilitation facilities with multidisciplinary teams to facilitate the patients' rapid mobilization and return to normal activities. Unfortunately, this progression can be delayed or prevented secondary to the formation of HO. Bony exostoses can impede the fit of the prosthesis or joint movement, cause considerable pain, and increase the likelihood of infection because of frank ulceration of the overlying skin. Excision of these symptomatic lesions may be required, thus increasing patient morbidity.[6] Therefore, there is a recognized need to elucidate the risk factors for development of HO and minimize its development and progression.

There is substantial literature on HO in the other trauma populations.[1,12–26] Evidence supports the hypothesis of a systemic metabolic alteration caused by the geographically dissociative occurrence of HO.[12] In the presence of a specific lesion, it is believed that trauma triggers a series of events within the wound progressing from osteoid formation to full calcification within a matter of weeks. The rate of bone formation is almost three times that of normal bone with twice the osteoclastic density; thus, the bone is highly metabolically active.[13] However, HO has been infrequently reported on explicitly in combat-related amputees. The development of HO in the residual limb of these patients has been recognized for many years, but there is an absence of data on the possible etiologic factors. A recent report on HO in US military personnel[5] demonstrated significant predictors of development of HO to be the final amputation level within the initial ZOI and a blast MOI. This report identified differences in the severity of HO between none to mild and moderate to severe with regard to number of procedures undergone by the patient and the time to closure of the overlying wound.

This study is the first direct comparison on the potential etiologic factors for the development of HO in UK and US Armed Forces combat-related amputees. Although there were no significant differences in the overall prevalence of HO or the rate of severe HO between the two groups, the percentage of patients with severe HO in group 1 (8.57%) is half that in group 2 (16.43%).

There was a significant association in group 2 between blast injury and the development of HO.[5] This association fits with the hypothesis that the significant tissue damage from

TABLE 4. Group 1 Analysis of Associations Between Development and Severity of HO and Debridements and Days to Closure

	HO	None	Mild	Moderate	Severe	None vs. Rest	None/Mild vs. Moderate/Severe
No. irrigation and debridements	Mean	3	5.375	3.375	6.3	0.078	0.34
	Median	1	5.5	2	7		
	Range	1–9	1–9	1–8	5–7		
No. days from injury to closure	Mean	10.4	19.125	8.1	35.67	0.054	0.42
	Median	4	18	4	39		
	Range	2–40	9–57	3–20	28–40		

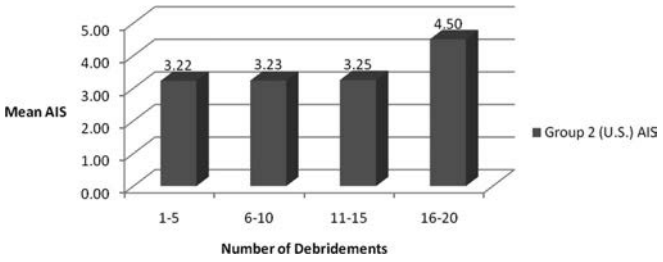

Figure 4. The association between EAIS and the number of debridements: no difference in EAIS between the groups ($p = 0.2455$).

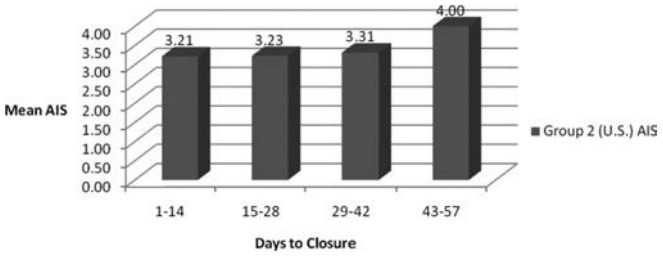

Figure 5. The association between EAIS and days to closure: no difference in EAIS between the groups ($p = 0.2656$).

such an injury triggers a series of local and systemic events leading to the formation of HO within the lesion. There was a correlation between greater numbers of blast limbs and group 1, although there was no correlation between MOI and the development of HO in this group. However, there was a significant association between increasing ISS and both the development and severity of HO. This finding has been observed in previous studies.[14] Because the ISS is a reflection of the overall injury load on the patient, this finding may substantiate the theory that there is a generalized metabolic disturbance with an increase in circulating cytokines (such as interleukins 4 and 13, both of which are chemotactic for osteoblasts) and other inflammatory or humoral mediators. These could potentiate the migration of mesenchymal cells, which are then induced to mature into osteoprogenitor cells by local molecules.[15,16]

There were significantly more amputations in total and, also, specifically in blast-injured limbs within the ZOI in group 2. In this group, a significant association was found between amputation in the ZOI and the development and severity of HO.[5] No such association was found in group 1, even when MOI was also considered; but the smaller number of patients in group 1 may have limited our power to detect such relationships. Debridement should be early and aggressive; however, provided that good wound care and adequate resuscitation are given, some recovery of seemingly traumatized soft tissue is possible. Therefore, it is advocated that debridement should leave any tissue that is questionable to preserve as much as possible for later reconstruction. However, this strategy may lead to a local inflammatory response after considerable trauma that would trigger the development of HO if amputation in the ZOI meant that a certain amount of traumatized tissue was left in situ postdebridement. Certainly, there were significantly fewer amputations in the ZOI in group 1, where there was also a lower rate of severe HO. Again, this finding could not be substantiated in group 1 may be a reflection of the smaller numbers of patients.

In both groups, there was a strong trend toward development of HO with increasing numbers of debridements and time to closure of the overlying wound. This trend became significant when both groups were combined. Although one may think that it could be a reflection of the severity of the local injury sustained or the inflammatory response mounted in the patients with multiple injuries, requiring a larger number of operations to successfully manage the wounds, no association was found between either the ISS or the EAIS and the number of debridements or days to closure. It does indicate that there may well be a link between further traumatization of the soft tissue by debridement, pulsatile irrigation, or NPWT use and development of HO. There was no association in group 1 with the severity of HO as opposed to group 2, where significant differences were demonstrated between an increase in severity of HO and the number of procedures or time to closure.[5] This may be explained by the highly significant difference between the two groups in the "debridement density" (number of debridements per number of days to closure) in the moderate and severe HO subgroups. In fact, group 1 had an average of 0.28 debridement per day (or 1 debridement every 3.5 days) compared with group 2, which had an average of 0.376 debridements per day (or 1 debridement every 2.6 days).

There was a significant association between the use of NPWT and development of HO in group 1. As it is only used in specified patients in UK patients, unlike the US, where it is used almost universally, we could not perform a direct comparison because of the inconsistent reporting of NPWT use in the US records. If we assumed that all amputees received NPWT, the differences in HO would be highly significant (in numbers). For

a true indication of the association between NPWT and HO development, a comparison should be drawn between amputees treated with NPWT and matched controls not treated with NPWT. This comparison was not possible in group 1 because of the small number of patients in each subgroup.

No association was found between the development or grade of HO and the method of wound closure in both groups. However, there were significantly more direct closures in group 2 than in group 1. It may be that prolonged use of NPWT (more common in US practice) allows for more direct closures.

In agreement with numerous previous observations, we noted a strong association in group 1 between HO and severe head injury.[14,17,18] The pathogenesis behind this association is controversial but may involve disturbance to the hypothalamic-pituitary axis, which are rich sites for production of growth factors.[18] It may also be linked to a higher injury load (as previously discussed) and concurrent prolonged immobilization, which has also been demonstrated to be associated with development of HO.[21] It is highly likely that the patient would have undergone a longer period of ventilation, which has also been linked with HO formation, possibly because it can cause alterations in homeostasis (such as pathologic increases in calcium and phosphorous) and subtle acid-base balance changes.[18] Hyperventilation leads to respiratory alkalosis that can increase risk of salt precipitation within the tissue, which may serve as the nidus for later development of HO.[18] Finally, Reddi[22] showed that after brain injuries, bone morphogenetic proteins are capable of inducing local periarticular cells into osteoprogenitor cells. The data on head injuries were not available for group 2.

Although the association between burns and HO has been well documented, it was not demonstrated in this study,[1,12,19,20] probably because of the small numbers of patients ($n = 2$) with burns in group 1. It is believed to be a response to the systemic inflammatory response following the event because of the association between HO formation and both the overlying anatomic location of the burnt tissue and location at distant sites. The data on burns injuries were not available for group 2.

We have not commented on the difference in the rate of infections between the two groups as follow-up was <2 months in group 2 compared with ≥ 6 months in group 1. Infections were not shown to be associated with either the development or grade of HO ($p > 0.05$) in group 1. Localized infection after total joint arthroplasty[27] and systemic infection[23] have been previously documented to be associated with HO formation. Again, this infection would correlate to a change in metabolic conditions that could trigger HO formation. However, infection has also been shown to impair bone regeneration in preclinical trials[28] and can result in delayed or nonunion in clinical fracture healing.[29] This finding could be explained by evidence that an inflammatory cascade induces both osteoblast apoptosis and osteoclastogenesis.[24–26]

The limitations of this study are that it is a retrospective review with its inherent drawbacks and that the numbers in group 1 are relatively small in comparison with group 2. Although we have observed a similar incidence of the overall rate of HO in both groups, a noticeable decrease in the rate of severe HO in group 1 occurred. There were significantly more amputations in the ZOI, number of debridements, and excision of symptomatic lesions in group 2 than in group 1. In the subgroup analyses, correlations have been shown in group 1 to the development of HO with TBI, increasing number of debridements, increasing days until wound closure, and use of NPWT. In group 2, the development of HO was associated with final amputation level within the ZOI, blast MOI, number of procedures, and time to closure of the overlying wound. There is a possible agreement in the development of HO being linked to the severity and degree of repeated traumatization to the extremity wound and the overall injury load on the patient. However, the discrepancies between the two groups noted underline the clear need for a review of treatment modalities and management of the systemic metabolic response to major trauma to minimize the development of HO.

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DISCUSSION

Dr. Robert Roussel (US Army Institute of Surgical Research, Fort Sam Houston, TX): Thank you for the opportunity to review the article, "Comparison of Development of Heterotopic Ossification in Injured US and UK Armed Services Personnel with Combat-Related Amputations." This article is a retrospective review of the rates of heterotopic ossification (HO) between injured US and UK military.

The article is interesting and highlights some important questions regarding HO, causation factors, and differences in casualty management between the US and the UK. However, I recommend a major revision of the Results Section. It was extremely difficult to trace the data being presented in the Results section to the proper table or figure.

Please address the following comments:

1. In the Materials and Methods section, it would be helpful to have an idea of the time frame that this retrospective study covers.
2. In the Results section (describing rate of HO), it is not clear to me that the *p* values match those listed in Table 1. In addition, the percentages in the table do not match the percentages in the text and do not have the proper significant figures in either case.
3. In the Results section (Number of Debridements and Number of Days Until Wound Closure), the data in Table 4 are presented with no reference to the table.
4. In the Results section (Use of NPWT), the data in Table 2 are presented with no reference to the table.
5. In the Results section (Injury Severity Score), you refer to Table 2, but the data are in Table 3.
6. In the Results section (Group 1 Further Analysis), you refer to Tables 3 and 4, but the severe burn and TBI data are in Table 2.

Kate V. Brown (US Army Institute of Surgical Research, Fort Sam Houston, TX): Thank you for your instructive comments on the article entitled "Comparison of Development of Heterotopic Ossification in Injured US and UK Armed Services Personnel with Combat-Related Amputations: Preliminary Findings and Hypotheses Regarding Causality." They have helped me to revise the manuscript to a stronger article. I have responded to each comment in turn, as follows:

1. This article covers the time from 2001 to 2008; the text now reflects this time frame, including a breakdown of the US and the UK time frames.
2. The *p* values have been corrected and the percentages clarified in the Table 1.
3. Table 4 is now referenced.
4. Table 2 is now referenced.
5. The data in Table 2 have been clarified.
6. The data in Tables 3 and 4 have been clarified.